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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/591,447	06/09/2000	Steven Neville Chatfield	KCO1003US	4359

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EXAMINER	
HINES, JANA A	

ART UNIT	PAPER NUMBER
1645	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/591,447	CHATFIELD ET AL.	
	Examiner	Art Unit	
	Ja-Na A Hines	1645	

-- The MAILING DATE of this c mmunication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 June 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17 and 20-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17 and 20-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *5,6* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Amendment Entry

1. The amendments filed June 9, 2000, January 14, 2002, March 26, 2002 and April 11, 2002 have been entered. Claims 18 and 19 have been cancelled. Claims 3, 4, 6-7, 10-13, 15 and 17 have been amended. Claims 21-30 have been added. Claims 1-17 and 20-30 are under consideration in this office action.

Specification

2. The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1-17 and 20-30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a vaccine comprising an attenuated mutant of *Salmonella enteritidis* wherein the transposon was inserted in the *sur*A gene which promotes folding of extraperiplasmic proteins ompA, ompF and lamB and further

comprising heterologous antigens such as the protective fragment C domain of tetanus toxin, also known as BRD115 does not reasonably provide enablement for a vaccine comprising a pharmaceutically acceptable carrier or diluent and a bacterium attenuated by a non-reverting mutation in a gene encoding a protein which promotes folding of extracytoplasmic proteins. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The specification teaches that the specific the construction of a vaccine comprising an attenuated mutant of *Salmonella enteritidis* wherein the transposon was inserted in the *sur*A gene to promotes folding of certain extraperiplasmic proteins and further comprises a heterologous antigen such as the protective fragment C domain of tetanus toxin, also known as BRD115. See the specification at pages 17-20, wherein the specification discloses the specific bacterial strains, mutated genes, and their incorporation.

The instant specification fails to provide any experiments that show that such vaccines would be effective in protecting a human or other animal against a bacterial infection. The term "vaccine" encompasses the ability of the specific antigen to induce protective immunity to a gram-negative infection or disease induction. The vaccine art is highly unpredictable and the instant specification fails to provide any information that the recited attenuated live vaccine would provide any immunity to any type of patient against any type of bacterial infection. There are no immunological experiments provided to demonstrate that the claimed vaccines are capable of mounting an effective

immune response and more importantly, there are no challenge experiments to demonstrate that an animal immunized with the any type of bacterium would be protected from any bacterial infection. There is no teaching of generating non-reverting mutations or of a low reversion rate for the mutated bacterium used in a live vaccine. There are no protocols provided which demonstrate which bacterium would be effective in immunization, nor are their protocols detailing the amount of bacterium needed to mount a sufficient immune response. It is unclear that one of skill in the art could follow these general guidelines and achieve immunization against a bacterial infection. The specification does not provide substantive evidence that the claimed vaccines are capable of inducing protective immunity against bacterial infection and/or disease. This demonstration is required for the skilled artisan to be able to use the claimed vaccines for their intended purpose of preventing an infection. Without this demonstration, the skilled artisan would not be able to reasonably predict the outcome of the administration of the claimed attenuated live vaccines, i.e. would not be able to accurately predict if protective immunity has been induced against a bacterium.

The ability to reasonably predict the capacity of a single bacterial immunogen to induce protective immunity from in vitro antibody reactivity studies is problematic. Ellis exemplifies this problem in the recitation that "the key to the problem (of vaccine development) is the identification of the protein component of a virus or microbial pathogen that itself can elicit the production of protective antibodies" (page 572, second full paragraph). Unfortunately, the art is replete with instances where even well characterized antigens that induce an in vitro neutralizing antibody response fail to elicit

in vivo protective immunity. See Boslego et al. wherein a single gonococcal pillin protein fails to elicit protective immunity even though a high level of serum antibody response is induced (page 212, bottom of column 2). Accordingly, the art indicates that it would require undue experimentation to formulate and use a successful attenuated live or whole cell vaccine without the prior demonstration of vaccine efficacy.

The specification fails to teach the identity an attenuated live vaccine with the claimed characteristics. Furthermore, the specification fails to adequately disclose a description of the claimed vaccines, thus a skilled artisan would be required to de novo locate, identify and characterize the claimed vaccines with the recited abilities. Accordingly, this would require undue experimentation given the fact that the specification is completely lacking in teachings as to attenuated vaccines with the broadly claimed protection characteristics. Thus, the art indicates that it would require undue experimentation to formulate and use a successful attenuated live vaccine without the prior demonstration of vaccine efficacy.

There is no teaching within the specification of any other vaccines comprised of other bacterial strains with other genes encoding a protein which promoted folding of all extraperiplasmic proteins, even though the art teaches other genes are capable of promoting folding in some proteins. The specification fails to teach examples of any other vaccine comprising an attenuated bacterium that meet the limitations of the claims. There are no other representative examples of such vaccines within the specification. The specification appears to make the conclusion that any bacterium can be used without any substantiating evidence. Furthermore, the specification appears to

conclude that each and every extraperiplasmic protein has its folding promoted by said gene, when the art teaches that the folding several periplasmic proteins is independent of SurA (see Lazar et al., 1994). Therefore, the claims are only enabled for a vaccine comprising an attenuated mutant of *Salmonella enteritidis* wherein the transposon was inserted in the *sur*A gene that promotes folding of periplasmic proteins ompA, ompF and lamB and further comprising heterologous antigens such as the protective fragment C domain of tetanus toxin, also known as BRD115.

Applicants have provided no guidance to enable one of ordinary skill in the art how to make, without undue experimentation, a vaccine comprising an attenuated bacterium wherein the attenuation is by a non-reverting mutation in a gene encoding a protein which promotes folding of extraperiplasmic proteins wherein there is no guidance as to the nature and extent of the changes that can be made. Given the lack of guidance contained in the specification and the unpredictability for making such vaccines, one of skill in the art could not make or use the broad claimed invention without undue experimentation.

Furthermore, the specification fails to provide an enabling disclosure for the use of any vaccine comprising an attenuated bacterium that meets the limitations recited in the claims. Applicants' have provided no guidance to enable one of ordinary skill in the art as to how determine, without undue experimentation, other vaccines comprising attenuated bacterium. Given the lack of guidance contained in the specification and the unpredictability for determining a vaccine comprising an attenuated bacterium, one

skilled in the art could not make or use the broadly claimed invention without undue experimentation.

4. Claims 1-17 and 20-30 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a vaccine comprising a pharmaceutically acceptable carrier or diluent and a bacterium attenuated by a non-reverting mutation in a gene encoding a protein which promotes folding of any extracytoplasmic protein. However the instant specification does not provide for any vaccine comprising any attenuated bacterium with a gene that that encodes a protein which promotes folding of any extraperiplasmic proteins. The written description, in this case, only sets a vaccine comprising an attenuated mutant of *Salmonella enteritidis* wherein the transposon was inserted in the *sur*A gene that promotes folding of periplasmic proteins ompA, ompF and lamB and further comprises heterologous antigens such as the protective fragment C domain of tetanus toxin, also known as BRD115; and therefore the written description is not commensurate in scope with the claims drawn to a vaccine comprising a pharmaceutically acceptable carrier or diluent and a bacterium attenuated by a non-reverting mutation in a gene encoding a protein which promotes folding of every extracytoplasmic proteins.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (*See Vas-Cath* at page 1116). Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 115).

Thus, the structure of the vaccines comprising an attenuated bacterium is not defined. With the exception of an attenuated mutant of *Salmonella enteritidis* wherein the transposon was inserted in the *sur*A gene that promotes the folding of periplasmic proteins ompA, ompF and lamB and further comprising heterologous antigens such as the protective fragment C domain of tetanus toxin, also known as BRD115, the skilled artisan cannot envision the detailed structure of the encompassed bacterium, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of producing said bacterium. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The vaccine itself, along with the recited mutations and limitations are required.

Furthermore, In *The Reagents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus by only their functional activity does not provide an adequate written description of the

genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of examples, falling within the scope of the claimed genus. At section B(1), the court states that an adequate written description requires a precise definition, such as by structure, formula, chemical name, or physical properties, not a mere wish or plan for obtaining the claimed chemical invention.

Therefore a precise description of mutation that creates a vaccine comprising an attenuated bacterium is necessary. However, no disclosure, beyond the mention of a vaccine comprising an attenuated mutant of *Salmonella enteritidis* wherein the transposon was inserted in the *sur*A gene that promotes the folding of particular periplasmic proteins and further comprising heterologous antigens such as the protective fragment C domain of tetanus toxin, also known as BRD115 is made in the specification, as described the examples. This is insufficient to support the generic claims of a vaccine comprising a pharmaceutically acceptable carrier or diluent and a bacterium attenuated by a non-reverting mutation in a gene encoding a protein which promotes folding of each and every extracytoplasmic proteins as provided by the Interim Written Description Guidelines published in the June 15, 1998 Federal Register at Volume 63, Number 114, pages 32639-32645.

Therefore only a vaccine comprising an attenuated mutant of *Salmonella enteritidis* wherein the transposon was inserted in the *sur*A gene that promotes the folding of periplasmic proteins ompA, ompF and lamB and further comprising heterologous antigens such as the protective fragment C domain of tetanus toxin, also

known as BRD115 as made in the specification and described in the examples of the specification, but not the full breadth of the claims meets the written description provision of 35 USC 112, first paragraph.

5. Claim 2-17 and 20-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 2-17 and 21-29 are unclear. It appears that the dependent claims are referring to the vaccine of claim 1, however the phrase "a vaccine" in the dependent claims is confusing since it is not clear whether applicant means the vaccine of claim 1, another vaccine or any number of vaccines. It is suggested that the dependant claims recite "the vaccine."

6. Claim 20 is drawn to a method of raising an immune response, however it is unclear how to define "raising." It is unclear how to raise an immune response or what the raised immune response is compared to, in order to determine if the response was raised. It is unclear whether raising is equivalent to invoking an immune response. Therefore, the term is unclear.

7. Claims 28 and 29 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. There are no steps recited for the method of vaccinating

an animal. Thus the method of vaccination fails to incorporate the necessary steps and the claims are rejected.

8. Claims 28 and 29 are also vague and indefinite. The claims are vague because the claims do not clearly state what the method of vaccinating an animal is vaccinating against, at what dosage will the vaccine be administered or how the vaccine is administered. Therefore, the claims are vague and indefinite.

9. Claim 30 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: there are no manufacturing steps or process steps recited by the claim drawn to how to make the vaccine including the reagents necessary to manufacture the vaccine. The claim recites only a steps of "providing a bacterium" however, the manufacturing method does not recite dosage of the manufactured vaccine, nor does the claims recite how the manufactured vaccine will be delivered, i.e., in encapsulated form. Thus the method of manufacturing fails to incorporate the necessary steps. Thus, the claims are rejected.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 1-6, 11, 12-14, 21 and 30 are rejected under 35 U.S.C. 102(b) as being anticipated by Lazar et al.(1996). Lazar et al., disclose SurA assists the folding of *E.coli* outer membrane proteins. SurA is a periplasmic protein of E. coli that has sequence similarity to the prolyl isomerase parvulin (abstract). SurA is cytoplasmic peptidyl prolyl isomerase from *E. coli* (page 1770). The authors determined that efficient folding of three outer membrane proteins requires SurA in vivo, thus the authors concluded that surA assists in the folding of certain secreted proteins, ompA, ompF and lamB but not in four other periplasmic proteins (abstract). The authors constructed a surA deletion to avoid the appearance of revertants of the surA allele (page 1770). The colony of bacterial cultures comprising SurA mutants was grown in rich medium (page 1770).

The vaccine compositions recited in claims 1-6, 11, 12-14 and 21 appear to the same as those of the prior art reference because the structure produced by the prior art reference would be identical to the structure of the composition recited in the instant claims. The term "vaccine" is an intended use only. A recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claims. Thus Lazar et al., teach a pharmaceutically acceptable carrier or diluent and an attenuated bacterium attenuated by a non-reverting mutation in a gene encoding a protein which promotes folding of extraperiplasmic proteins. The method of manufacturing the vaccine recited in claim 30 is inherent based on the teachings

disclosed above because in a claim drawn to a process of making, intended use must result in manipulative differences as compared to the prior art. See *In re Casey,* 152 USPQ 235 (CCPA 1967) and *In re Otto*, 136 USPQ 458, 459 (CCPA 1963). No structural differences are recited in the vaccine compositions instantly claimed which would distinguish them from the prior art.

Therefore, Lazar et al., disclose a pharmaceutically acceptable carrier or diluent and an attenuated bacterium attenuated by a non-reverting mutation in a gene encoding a protein which promotes folding of extraperiplasmic proteins.

Prior Art

11. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Dougan et al., (US Patent 5,527,529) teach vaccines comprising attenuated *Salmonella* bacteria, methods of production, and pharmaceutical compositions. Missiakas et al., teach new components of protein folding in extracytoplasmic compartments of E.coli SurA, FkpA and Skp/OmpH. Rouviere et al., teach SurA a periplasmic protein that participates in the assembly of outer membrane porins.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ja-Na A Hines whose telephone number is 703-305-0487. The examiner can normally be reached on Monday-Thursday and alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on 703-308-3909. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Ja-Na Hines
August 21, 2002

NITA MINSFIELD
PRIMARY EXAMINER
8/22/02